Ladner et al. was enabled as of the priority date for the `063 continuation-in-part (CIP) application. The Office Action also provides specific comments to its interpretation of applicant's arguments. Applicant will address below each of the asserted points.

The Office Action initially sets forth general comments regarding applicant's contention that the Lander `063 CIP application lacks enablement. In this regard, the Office points out: (1) that applicant that an application may satisfy the enablement requirement although each and every embodiment within the scope of the claims are not enabled; (2) that there is no evidence of an enablement rejection in the `063 application, and (3) that the unpredictability of an invention requires that there be both no forethought to potential problems and that the unpredictability is associated with a part of the invention that is vital to the practice of the invention.

For a publication to anticipate a claimed invention, the disclosure of the publication must be enabled. *In re Borst*, 345 F.2d 851, 855 (C.C.P.A. 1965), *cert. denied*, 382 U.S. 973 (1966); *In re Legrice*, 301 F.2d 929, 936 (1962). The Lander `063 CIP application fails to enable the surface expression of a gene VIII fusion protein at least because it would require undue experimentation to determine which, if any, of the various purported signal sequence embodiments would work as described.

Applicant is not unaware that the enablement requirement of 35 U.S.C. §112, first paragraph, may allow for certain non-enabled embodiments. However, for cited art to be enabled it must teach the full scope of the invention sufficient to allow those skilled in the art to practice it without undue experimentation. Applicant's response at page 2, *citing In re Borst*, 345 F.2d 851, 855 (C.C.P.A. 1965), *cert. denied*, 382 U.S. 973 (1966); *In re Legrice*, 301 F.2d 929, 936 (1962); *Genentech, Inc. v. Novo Nodisk A/S*, 108 F.3d 1361 (Fed. Cir. 1997); *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360-61 (Fed. Cir. 1998); *Plant Genetics Systems, N.V. v. Dekalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003). Applicant maintains that there is insufficient guidance in the Ladner `063 CIP application with respect to a sufficient number of working species, if any, that enable the full scope of the cited art.

Although applicant gives due deference to the competency of the Office, the patentability of biotechnology inventions in 1990 was still a nascent art. There are numerous examples where an invention, and particularly a biotechnology invention has been held invalid for lack of enablement although the *ex parte* record may not have predicted such a result.

Finally, the law is clear with respect to the amount of permissible experimentation allowed before such experimentation required to practice the invention constitutes undue experimentation. Where the art is unpredictable, as with the `063 application, gaps in the disclosure amount to more than omission of minor details and fail to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. *Adang v. Fischhoff*, 286 F.3d 1346, 1358 (Fed. Cir. 2002); *accord, Genentech*, 108 F.3d at 1367-68 (an enabling description for unpredictable technology must provide those skilled in the art with a specific and useful teaching). Further, in *Genentech*, the Federal Circuit held that a cleavable fusion protein for human growth hormone was not enabled as a matter of law because the specification provided only a starting point and a direction for further research. 108 F.3d at 1364-66.

Forethought as to potential problems is insufficient to satisfy enablement. Instead, there still must be sufficient guidance to practice the invention without undue experimentation. The required guidance is not satisfied where, as here, there is hypothetical speculation inviting one to experiment as well as inconsistent and contradictory descriptions as to what results were or were not obtained. Further, the requirement of a signal sequence for the gene VIII chimeric proteins described in the `063 application is very relevant to the practice of the invention because it is a prerequisite for achieving surface expression, production and retention of a mature gene VIII fusion protein.

Applicant's remarks with regard to specific points set forth in the Office Action alleging that the `063 application satisfies the enablement requirement of 35 U.S.C. §112, first paragraph, are provided below.

The Office Action asserts that the `063 application provides a solution to the hypothetical problem regarding use of a heterologous signal sequence to target surface

expression of gene VIII fusion proteins because the `063 application provides a specific working example using the *phoA* signal sequence.

Applicant points out that its previous response did not argue that there was a hypothetical problem associated with the use of a "heterologous signal sequence." Instead, applicant's contention and submitted evidence was directed to the point that the `063 application lacked sufficient guidance as to whether any signal sequence would successfully direct surface expression of a gene VIII fusion protein - heterologous or homologous. The totality of the evidence shows that those skilled in the art could not rely on the descriptions in the `063 application because they are significantly contradictory and inconsistent so as to raise serious concerns by one skilled in the art. Such concerns are sufficient to question whether any purported guidance offered in the `063 application would yield the alleged result without undue experimentation.

Applicant pointed out in its previous response that the `063 application describes in one passage that an embodiment works; describes in another passage experiments that may be tried if the embodiment doesn't work, and in yet another passage that the embodiment doesn't work. In light of these inconsistent descriptions, there is no reason why one skilled in the art would select any single description, out of the several hundred pages of the `063 application, and choose that isolated description to conclude that a particular embodiment worked as described. Instead, one skilled in the art would conclude that the application lacks consistent guidance and that any results obtained would similarly be unpredictable.

The Office Action similarly asserts that the `063 application does not provide an invitation to experiment because the *phoA* signal sequence is purportedly described to have worked. As applicant pointed out previously and again above, the fact that one description, buried within other contradictory descriptions, relevant to which signal sequences will work does not provide adequate guidance to overcome the doubts one skilled in the art would have when the teachings of the `063 application are viewed as a whole. The Office Action fails to point to why this purported result should be given weight over the various other inconsistent and contradictory descriptions relevant to successful expression of a gene VIII fusion protein.

Further, the Office Action states that the '063 application clearly indicates that:

> (a) the signal sequence is not the important feature of the invention, going so far as to suggest that multiple different sequences can be substituted for the signal sequence and (b) that the primary feature of the invention is the retention of the mature coat protein (see applicant's Exhibit 3, lines 7-9 and 10-15). Ladner discusses that the purpose of the signal sequence is simply the targeting of the surface expression of the gene VIII fusion protein, and the skilled artisan would clearly recognize that substituting any known signal sequence would not incur undue trial and error experimentation. Applicant is respectfully reminded that this method is not directed to finding new signal sequences, but instead to the surface expression of a fusion protein using known signal sequences.

Office Action at pages 6-7.

Applicant respectfully points out that the contentions made in this paragraph fail to address the issue of non-enablement as Applicant set forth in the previous response. At page 5 of the previous response, applicant stated that the description of working chimeric gene VIII fusion proteins is speculative because Ladner acknowledges that it is unknown whether the gene VIII fusion proteins will work as described since it discusses alternatives that can be attempted if "none of the described approaches produces a working chimeric protein." Applicant's response mailed May 19, 2003, paragraphs 1-2, *quoting* Exhibit 2, page 205, lines 15-21 (*see also* Exhibits 3 and 4, and applicant's response at page 5, paragraph 3). The approaches described by Ladner are directed to the use of a signal sequence which is necessary to successfully direct surface expression of a gene VIII fusion protein.

Therefore, the lack of enablement is directly related to the successful use of a working signal sequence that directs surface expression of a gene VIII fusion protein. There can be no retention of the mature coat protein, and achievement of the purpose of Ladner's purported invention, unless there first is successful targeting and expression on the surface of a bacteria or bacteriophage of a gene VIII fusion protein. Targeting requires a working signal sequence.

Ladner himself states this at page 10 of applicant's Exhibit 3, (also cited by in the Office Action), when he states:

> It is sufficient that the signal peptide directs the fusion to be secreted through the lipid bilayer.

Again, there can be no achievement of the requirement to direct the fusion through the lipid bilayer if the description within the application is insufficient to teach which signal sequence will work without undue experimentation. The `063 application fails to provide such predictability because there is no indication as to which of the inconsistent and contradictory results are to be given more or less weight compared to others. Therefore, the contention at page 7 of the Office Action that the `063 specification serves as sufficient guidance since it indicates that other signal sequences may be substituted so long as the mature gene VIII coat protein is maintained fails to support enablement because it evades the issue. The mature coat protein will never be produced so that it can be "maintained" if the signal sequences does not work.

Paragraphs 3-5 at pages 7 and 8 of the Office Action again allege that applicant appears to argue that all embodiments lack enablement if one embodiment lacks enablement and also that an isolated description to *phoA* signal sequence, out of the many descriptions, provides sufficient guidance to enable the full scope of the invention. The points set forth above are reiterated here as support.

The arguments set forth by applicant should not be interpreted to support the proposition alleged in the Office Action. As stated previously, the totality of the teachings in the `063 and `160 applications suggest nothing more than a mere invitation to experiment because they are inconsistent and contradictory. As such, the descriptions in the `063 application are unreliable and fail to convey what sequence constitutes a predictable signal sequence that will successfully direct surface expression of a gene VIII fusion protein. Reliance on the *phoA* signal sequence by the Office is misplaced because there is nothing in the `063 application that lends greater weight to its description over any of the other descriptions. The *phoA* signal sequence should not be construed as "clearly enabled" in light of the various other inconsistent and contradictory assertions in the `063 application, some of which purport that other signal sequences work as well. In this regard, the selection of the *phoA* description, out of the many descriptions, appears to be biased by hindsight in light of the current record.

Paragraph 6 of the Office Action alleges that the Markland publication is not found to be contradictory to the `063 application. In this regard, the Office Action asserts that

applicant's argument regarding quantitative inconsistencies between the `063 application and the Markland et al. publication is inapplicable because the expression levels result from two different constructs.

The Office's interpretation of applicant's response appears to be incorrect. The relevant comparison in applicant's response was not directed to the expression levels of two different gene VIII constructs. In this regard, the comparison between the Markland et al. publication and the results purported to have been obtained in the `063 application correspond to the same construct expressed in the same bacterial strain. For example, applicant stated:

> The Markland et al. article shows the actual expression levels of the signal sequence variants presented in Table 108 of the '063 application (Exhibit 8). . . . The gene VIII results presented in line 10 of the Table correspond to the duplicates in lanes 9 and 10 of Figure 2 in the Markland et al. article. Similarly, line 11 from Table 108 corresponds to the duplicates in lanes 5 and 6, whereas line 15 of Table 108 corresponds to the duplicates in lanes 12 and 13.

Applicant's response, paragraph bridging pages 11-12.

Therefore, the inconsistencies between the Markland et al. publication and the `063 application are directly relevant to the purported teachings of the `063 application because Marklead et al. reports on the same expression experiments as the `063 application, but differs significantly in the describe results. Briefly, applicant pointed out these inconsistencies in the previous response when it stated:

> [T]he actual expression data in Markland et al. of the signal sequence variants appears not to correlate with their qualitative description presented in Table 108.

and,

> First, the MB42 construct is shown by a "+" to be processed in line 11 of Table 108. Figure 2, lanes 5 and 6 of Markland et al. do not appear to show any such processed species. Second, the alleged processed species shown by a "+/-" in line 10 is inconclusive based on the data shown in lanes 9 and 10.

Applicant's response at page 11.

The above passage from applicant's previous response is a direct comparison between the same constructs. Accordingly, applicant did not make irrelevant comparisons as asserted in the Office Action.

Moreover, the interpretation in the Office Action that "any perceived error in the quantitation between the `063 application and the Markland publication . . . does not change the fact that the *phoA* sequence resulted in surface expression of the gene VIII fusion protein in both the `063 application and the Markland reference" again evades the issue. As stated previously, there are numerous inconsistencies within the `063 application that raise serious doubts as to whether any purported descriptions in the `063 application can be practiced as described. Such doubts are sufficient to raise a serious expectation of undue experimentation based on a reading of the `063 application.

The Markland et al. publication is offered as support of this conclusion because it is similarly inconsistent with both the descriptions of the purported results as well as to the purported quantitation.

Finally, it was not until the filing of the final CIP application on March 1, 1991, that the Ladner patent attempted to correct the various inconsistencies and contradictory descriptions. Because the descriptions within the previous filings are inconsistent and contradictory they cannot be relied upon to enable the surface expression of a gene VIII fusion protein. Accordingly, the Ladner patent should at best be considered to have provided an enabling disclosure not earlier than the last CIP filing of March 1, 1991.

Applicant, on the other hand, describes and claims gene VIII fusion proteins that can be expressed on the surface of a filamentous bacteriophage from a compatible host cell. In light of the inability of the '063 application to provide sufficient teachings for one skilled in the art to express gene VIII fusion proteins without undue experimentation as of its filing date of March 2, 1990, the cited '409 patent cannot anticipate claims 88-91 because it was not enabled prior to Applicant's priority date of September 28, 1990. In re Borst, 345 F.2d at 855, 145 U.S.P.Q. at 557 (accord Minnesota Mining and Manufacturing, Co. v. Chemque, Inc., 303 F.3d

1294, 1301, 1306, 65 U.S.P.Q.2d 1270 (Fed. Cir. 2002)). Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be removed.

Obvious-Type Double Patenting Rejections

Claim 1 stands rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 29 of U.S. Patent No. 6,258,530 ("the `530 patent"). The Office Action appears to assert that claim 1 of the `530 patent is a species of pending claim 1 and that claim 29 of the `530 application is sufficiently generic that together they render obvious pending claim 1.

Applicant maintains that claim 1 is unobvious in light of claims 1 and 29 of the `530 patent. Claim 1 of the above-identified application is directed to a plurality of cells containing a diverse population of expressible oligonucleotides having a desirable bias of random codon sequences produced from random combinations of first and second oligonucleotide precursor populations. In contrast, claim 1 of the `530 patent is directed a plurality of cells where oligonucleotides are linked to a suppressible stop codon and to the major coat protein of a filamentous bacteriophage and where expression elements direct the expression of oligonucleotides from a filamentous bacteriophage vector as a major coat protein fusion in a suppressor host or as a soluble peptide in a non-suppressor host. Claim 29 of the `530 patent is directed to a population of oligonucleotides encoding completely random amino acid sequences.

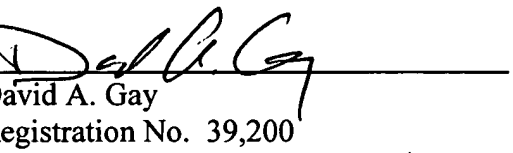
Applicant maintains that claims 1 and 29 of the `530 patent do not render claim 1 of the instant application obvious at least because claims 1 of the `530 patent is directed to particular and distinct modes of expression that result in alternative expression of a peptide when used in conjunction with specific types of procaryotic host cells. Moreover, claim 29 is not directed to a desirable bias of random condon sequences. Instead, claim 29 is directed to unbiased amino acid sequences. Accordingly, it would not be obvious to one skilled in the art to produce a plurality of cells as claimed in the instant application in light of the particularities of claims 1 and 29 in the `530 application. Applicant therefore, respectfully requests that this ground of rejection be removed.

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned attorney if there are any questions.

Respectfully submitted,

Date: February 11, 2004



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